

MAR 29 2007

REMARKS

Reconsideration of this application, as amended, is respectfully requested.

I. Status of the claims

Claims 1-28, 67-77, 79, and 122-125 were pending in this case. Claim 125 has been allowed. Applicants respectfully submit that the remaining claims in this application are allowable as well for reasons discussed below.

Consideration and entry of this response is respectfully requested. The response does not raise any new issues nor would create any burdensome search from the Examiner.

II. Rejections under 35 U.S.C. § 103 based on Chu and Shultz

Claims 1-3, 6-12, 16-28, 67-77, 79, and 122-124 were again rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu et al. U.S. Patent no. 6,174,704 ("Chu") in view of Shultz. U.S. Patent no. 6,242,235 ("Shultz"). The basis for the rejection is described on pages 2 and 3 of the Office Action. Specifically, the Examiner states that Chu teaches compositions comprising aqueous solutions of alkylglycoside or alkylthioglycoside in amounts ranging from 0.5 to 5% w/v; that buffers such as TRIS or HEPES can be used to maintain a 7-8 pH value; that lysozyme can be included in the solutions; that the solutions can be used to prepare, extract, detect, purify and collect isolated proteins; that protein products can be incubated with nickel charged resins and purified on resins; that the aqueous solutions may be used for lysing cells in a protein extraction process; and that octylthioglucoisides can release proteins from cell membranes or cell walls. See pages 4 and 5 of the Office action. The Examiner then goes on to detail what is missing in Chu, namely the disclosure of inclusion of cationic surfactants comprising ethoxylated amine such as Tomah E-18-15 or Tomah E-18-5. The Examiner then uses Shultz to create the claimed composition from the prior art. On this basis, the Examiner alleges that the claimed composition is *prima facie* obvious in view of Shultz and Chu. The Applicants respectfully traverse this rejection.

A. The Action failed to establish a prima facie case of obviousness because there is no motivation to combine the cited art.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2142 (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)).

A §103 rejection based on a combination of references requires a *motivation in the art*, not just a restatement of the beneficial result that was foretold by the Applicant's disclosure and claims. Regarding the Examiner's hindsight approach, the Court of Appeals for the Federal Circuit has said the following:

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."

Most if not all inventions arise from a combination of old elements. Thus, every element of a claimed invention may often be found in the prior art. However, **identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention.** Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

In re Kotzab, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citations omitted).

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness over Chu in view of Schultz because one of skill in the art would not be motivated to combine Chu and Schultz. Applicants submit that the section 103(a) rejection is based on improper hindsight reconstruction of the claimed invention based on teachings in the Applicants' disclosure and not the cited art. Chu merely relates to lysis of host cells and extracting proteins of interest therefrom. See abstract. Specifically, Chu employs a reagent solution consisting

essentially of an alkylglycoside or alkylthioglycoside. See col. 1, lines 51-55. Contrary to the Examiner's position, there is no teaching or suggestion in Chu that any protein stabilization is necessary or even desirable to do. Indeed, Chu is completely silent with respect to a composition having "at least one surfactant having a hydrophobic-lipophilic balance value in the range from about 11 to about 16" and further in combination with "at least one cell membrane altering compound." See claims 1 and 67. A disclosure of a solution consisting essentially of alkylglycoside or alkylthioglycoside with added buffers and/or lysozyme is not a disclosure or suggestion of the composition and method as presently claimed. That Chu indicates, generally, that other constituents can be included which do not adversely affect the benefit's of Chu's solution can be included is at most an invitation to investigate a plethora of compounds. The statement is not a teaching or suggestion that the presently recited surfactants would be useful in his composition. There is nothing in Chu that would provide an ordinary skilled artisan with any motivation to make the presently claimed composition with the expectation that such composition would provide the surprising and unexpected results discussed below and in the previous response of October 30, 2006. Shultz adds nothing that remedies the deficiencies in Chu's teachings.

Shultz merely relates to compositions for stabilizing proteins, and is limited to cationic surfactants. Moreover, Shultz does not actually teach or suggest cell lysis nor does he teach or suggest that this would be necessary or desirable to do.

Selection of a material such as a surfactant to provide enzyme stability does not automatically presume that it will also provide effective lysis. Some surfactants can form micelles that may act to provide additional stabilization of cellular membrane proteins, thus making extraction more difficult. Accordingly, without a suggestion of lysis in Shultz, one of ordinary skill would not be motivated by Shultz's teachings concerning protein stabilization to include a surfactant (e.g., Tomah E-18-15 or E-18-5) in Chu's lysis reagent and thus arrive at the presently claimed invention with any reasonable expectation of success. Accordingly, withdrawal of the §103 rejection based on Chu in view of Shultz is respectfully requested.

Federal case law has repeatedly explained the importance of the motivation to combine as a safeguard against impermissible hindsight. See *In re Kotzab*, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) and *DyStar Textilfarben GmbH & Co Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006). In fact, *DyStar* further explained that the motivation-to-combine

inquiry prevents statutorily proscribed hindsight reasoning when determining obviousness. Moreover, the motivation-to-combine test also informs the Graham analysis by implementing the recognition of the importance of guarding against hindsight when determining obviousness. *DyStar*, at 1361.

B. The Action failed to establish a prima facie case of obviousness following the Graham Factual Inquiries.

The Supreme Court in *Graham* set out the factual inquiry, which the Patent Office must follow in determining obviousness. *Graham v John Deere Co.*, 383 U.S. 1, 17 (1966). The inquiry includes (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations.

(1) The Scope and Content of the Cited References

Chu merely relates to lysis of host cells and extracting proteins of interest therefrom. Specifically, Chu employs a reagent solution consisting essentially of an alkylglycoside or alkylthioglycoside. However, there is no teaching or suggestion in Chu that any protein stabilization is necessary or even desirable to do. Shultz merely relates to compositions for stabilizing proteins, and is limited to cationic surfactants. Moreover, Shultz does not actually teach or suggest cell lysis or protein extraction nor does he teach or suggest that this would be necessary or desirable to do.

(2) The Differences Between the Cited References and the Claims

The present claims are directed to cell lysis composition comprising at least one surfactant having hydrophilic-lipophilic balance value in the range from about 11 to about 16 and at least one cell membrane altering compound. Claims 2, 3, 6-12, 16-28, and 125 further define different component. Claims 67-77, 79, and 122-124 are directed to kits containing the composition. The present claims, considered as a whole, differ from cited art in that Chu does not teach or suggest a surfactant for effective cell lysis. As such, Chu does not provide any kind of motivation to combine Shultz to arrive at the claimed composition for effective cell lysis comprising a cell membrane

altering compound and a surfactant having a hydrophilic-lipophilic balance value in the recited range.

(3) Level of Ordinary Skill in the Pertinent Art

Both Chu and Schultz are at least of the level of ordinary skill in the art, yet the claimed invention did not occur to either one of them. Nothing in Chu or Schultz provides a motivation to combine the references to arrive at the claimed composition. Additionally, there is nothing implicit in the knowledge of one of ordinary skill in the art to motivate the combination of Chu and Schultz to arrive at the claimed invention.

Accordingly, withdrawal of the § 103 rejection of the claims based on Chu in view of Schultz is in order and is respectfully requested.

C. The claims are non-obvious over cited art because of unexpected results.

Applicants further submit that the claimed invention is not obvious over Chu in view of Shultz, because the instant application disclosed unexpected results for the claimed composition that are not taught or suggested in either of these references, alone or in combination. Unexpected results provide objective evidence of nonobviousness and strong support for a conclusion of nonobviousness. *U.S. v. Adams*, 383 U.S. 39, 51-42 (1966); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). A showing of unexpected results is to demonstrate that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected. *In Re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). The principle behind the rule of allowing the use of unexpected results to rebut an obviousness rejection is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. *Id.*

The instant application discloses the results of the levels of a reporter protein (luciferase) released from cells lysed by a cell membrane altering compound alone, by at least one surfactant alone, and by the combination of the two. Chu discloses the use of a cell membrane altering compound to lyse the cell. Schultz discloses the use of a surfactant to stabilize protein activity. The Applicants had unexpectedly discovered that cell lysis composition containing both a cell

membrane altering compound and a surfactant produced a synergistic effect much greater than that obtained with each reagent alone.

Table A below illustrates the unexpected results of Example 3. Table A shows that the combination of a cell membrane altering compound polymyxin B and a surfactant, such as Tomah E18-15 or Rhodameen, dramatically increases the release of luciferase to the supernatant. The synergistic effect results in at least a 178 fold increase in the percentage of luciferase released to the supernatant, comparing to the percentage of luciferase released using polymyxin B, Tomah E18-15, or Rhodameen alone.

TABLE A

Source	Sample	Composition	Overall ¹ Luciferase Activity	Supernatant Luciferase Activity	% of release
Example 3	K	Polymyxin B	4150.4	2.4	0.057
			6560.8	3.8	0.057
	G	Tomah E18-15	6203.5	2.5	0.040
			7603.1	2.1	0.027
	R	Polymyxin B, Tomah E18-15	984.8	144.2	14.6
			897.1	162.5	18.1
	D	Rhodameen	7223.6	4.6	0.063
			8014.6	6.6	0.082
	O	Polymyxin B Rhodameen	557.8	83.6	14.9
			366.1	152.0	41.5

¹ The value of overall luciferase activity is obtained by combining the supernatant sample readings with the pellet sample readings.

Even if, for the sake of argument only, there is any suggestion in Chu to include a protein stabilizing agent such as surfactant as a cell lysis composition, it does not follow that the unexpected results obtained from the claimed composition could have been anticipated by one of skill in the art. The test of obviousness is whether the invention as a whole would be obvious, including the nature of the results obtained. The court has stressed that in determining obviousness of the claimed product, the inquiry must not focus solely on the product created, but also on the obviousness or nonobviousness of its creation. *General Motors Corp. v. U. S. International Trade Commission*, 687 F.2d 476, 482-83 (C.C.P.A. 1982). Neither Chu nor Schultz recognizes the synergistic effect of the combination of a cell membrane altering compound and surfactant on cell lysis and protein extraction. Neither Chu nor Schultz

appreciates the claimed invention. One of skilled in the art would have found the results demonstrating the synergistic effect on cell lysis surprising and unexpected, and thus would have found the invention non-obvious.

The Examiner asserts that the composition one of skill in the art would have arrived by combining the teachings of cited art would have necessarily had the same unexpected results as possessed by the claimed composition. See page 8 of the Office Action. The assertion is precisely the product of impermissible hindsight reconstruction. Certainly, in hindsight there exists a route to a particular result. However, the disclosure in Chu or Schultz, alone or in combination, in no way foresees the unexpected results obtained by the claimed composition.

The Court has made it clear that "the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966) (emphasis added). The unexpected synergistic effect was previously unknown. The Examiner has not provided any basis in fact or technical reasoning indicating that the advantage illustrated by the unexpected results was known to one of skill in the art at the time of the invention, or is taught or suggested by the cited art. The Federal Circuit has explicitly rejected the retrospective view of inherency as employed by the Examiner as a substitute for some teaching or suggestion supporting an obviousness rejection. See *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993). Such a retrospective view of inherency would completely forestall any use of unexpected results as evidence to rebut an obviousness rejection, the use of which has been explicitly sanctioned by the Supreme Court. See 383 U.S. at 51-42 (1966). The Examiner has failed to provide any technical reasoning as to why and how one skilled in the art would have made such a leap of logics in arriving at the claimed invention based on Chu and Schultz, without the benefit of the disclosure of the instant application.

In view of the above discussion, the Applicants submit that Chu and Shultz, either alone or in combination, does not teach or suggest the surprising results obtained by the claimed composition. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejection under U.C.S. 103(a).

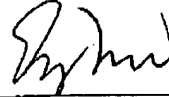
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IV. Conclusion

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes this would be helpful in expediting the allowance of this application.

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Respectfully submitted,



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